REMARKS

Upon entry of this Amendment, claims 68-74, 91, and 92 will be pending.

The Examiner has withdrawn claim 90 as drawn to a non-elected invention. Accordingly, Applicants have canceled claim 90 without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claim in a related application.

The claims have been amended to more particularly point out and distinctly claim that which Applicants regard as the invention, to clarify that the screening methods of the present invention are characterized by the level of Notch protein or "molecule having antigenicity of a Notch protein". The amendment to the claims is supported in the specification as filed at page 48, lines 16-19.

2. The Examiner's Rejection Under 35 U.S.C. § 112, First and Second Paragraphs

Claims 68-74, 90 [sic], 91, and 92 are rejected under 35 U.S.C. § 112, first and second paragraph for lack of enablement and/or for failing to particularly point out and distinctly claim the invention, because, according to the Examiner:

> The specification defines the terms "Notch protein" and "Notch derivative" but the definitions are so broad that the terms actually encompass epidermal growth factor (cysteine-rich EGF repeats are characteristic of both EGF and the various Notch homologs). The specification is not enabling for correlating the presence of a malignancy, disease or disorder of the nervous system or benign disproliferative disorder with the levels of "Notch proteins" or "Notch derivatives" as those

terms are broadly defined. The term "Notch homolog" is more descriptive of the proteins actually associated with malignancy, disease, or disorder of the nervous system or benign disproliferative [sic] disorder.

Applicants respectfully traverse this rejection with respect to the term "Notch protein" and submit that the Examiner's interpretation of the scope of this term exceeds its broadest reasonable construction in view of the teachings of the specification. Applicants further submit that the amendment to the claims has obviated the Examiners rejection with respect to the phrase "Notch derivative."

It is axiomatic that, in proceedings before the Patent and Trademark Office, claims in an application are to be given their broadest reasonable interpretation consistent with the specification and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art. *In re Sneed and Young*, 218 U.S.P.Q. 385, 388 (Fed. Cir. 1983). Applicants submit that the term "Notch protein" is used throughout the specification to refer to the Drosophila Notch protein and its various homologs, such as the human hN and *TAN-1* homologs, that are naturally existing proteins, consistent with common usage in the art. For example, the description of Figure 13, at page 10, lines 7-14 of the specification is captioned "Aligned amino acid sequences of Notch proteins of various species." Included in this figure are "Notch proteins" encoded by the human *Hn* and *TAN-1* homolog, as well as the "Notch protein" in Xenopus and Drosophila.

The Examiner alleges that the terms "Notch protein" and "Notch derivative" are so broad that the terms actually encompass epidermal growth factor because, "cysteine-rich EGF repeats are characteristic of both EGF and the various Notch, homologs."

Applicants disagree. Applicants submit that one skilled in the art, in view of the teachings of the specification and common usage in the art, would clearly know that epidermal growth factor is not a Drosophila Notch protein nor is it encoded by a Notch homolog of another species and, therefore, it does not qualify as a "Notch protein." Applicants submit that the meaning of "Notch protein" is clear to one skilled in the art, and that the claims are enabled for this meaning of "Notch protein" as recited in the claims, as evidenced by the ample guidance given in the specification for conducting the claimed methods and the data confirming the utility thereof (see Sections 5.6, 10, and 10.1 of the specification).

With respect to the recitation of "Notch derivative", Applicants have amended the claims to replace the recitation of derivative with a molecule that can be bound by an anti-Notch antibody, *i.e.*, a molecule that displays the antigenicity of a Notch protein. Applicants point out that this recitation is fully enabled as demonstrated, *inter alia*, by Sections 10 and 10.1 of the specification in which increased levels of a molecule that binds to anti-Notch antibody is shown to occur in tissue samples of various cancers.

As demonstrated by the disclosure of the instant specification, in order to carry out this embodiment of the

claimed methods, it is not necessary even to identify or characterize the molecule reactive with the anti-Notch antibody; all that is needed is to measure the binding to the antibody of a molecule in the sample, which molecule, by virtue of its binding to the antibody, must have the antigenicity of a Notch protein.

Applicants respectfully assert that they have obviated the rejection of the claims under 35 U.S.C. § 112, first and second paragraph, as a consequence of the amendments and arguments above. Accordingly, Applicants respectfully request withdrawal of the rejection.

3. The Rejection Under 35 U.S.C. § 103

Claims 68-74, 91 and 92 are rejected under 35 U.S.C. § 103 as being obvious over Ellisen *et al.* (1991, *Cell* 66:649-661) ("Ellisen").

Applicants respectfully traverse this rejection.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Fine*, 837 F.2d

1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed Cir. 1988).

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with a suggestion of the claimed composition or method. *See In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993).

Ellisen does not render the instantly claimed invention obvious. Moreover, Applicants submit that Ellisen is an improper basis to support an allegation of *prima facie* obviousness. Accordingly, Applicants request that this rejection be withdrawn.

The Examiner contends that Ellisen suggests that alterations in the structure and/or expression of *TAN-1* contribute to transformation or progression in some T cell neoplasms, and that *TAN-1* is also involved in neural differentiation.

The Examiner alleges that:

> [I]t would have been obvious for one of ordinary skill in the art to have screened for malignancy, diseases, or disorders of the nervous system or benign disproliferative [sic] disorders by detecting alterations in Notch protein expression because Ellisen et al suggest that there is a correlation between aberrant Notch expression and malignancy, and disorders of the nervous system.

Applicants disagree and submit that Ellisen does not teach or suggest the diagnostic methods of the present invention of screening for the presence of a malignancy,

disease or disorder of the nervous system, or benign dysproliferative disorder, characterized by an increased or aberrant level of Notch protein or molecule having the antigenicity of a Notch protein in a patient.

Applicants point out that Ellisen teaches that certain T lymphoblastic leukemic cells contain a translocation resulting from breakpoints within an intron of *TAN-1* and that this translocation results in the truncation of *TAN-1* RNA.

Ellisen cannot render the claimed invention obvious because the effect of a translocation within a gene upon the expression of the product of that gene is unpredictable. Such translocation may result in an increased expression of the product resulting from, for example, an increased transcription of the RNA encoding the functional portion of the protein as observed in the translocation associated activation of *c-myc* expression in Burkitt lymphomas (See, *e.g.*, Croce, C., 1987, *Cell* 49:155-156, attached hereto as Exhibit A). Alternatively, the translocation may lead to a decrease or absence of some of the regions of the protein resulting from, for example, the formation of a fusion protein as seen in a mutation of the tumor suppressor PML, resulting from the T(15:17) translocation (See, e.g., Borrow and Solomon, *Bailliere's Clinical Haematology* 5:833-856, attached hereto as Exhibit B). Furthermore, the translocation may not impact upon the expression level of the gene product, as demonstrated for example, by the observation that the constitutive elevated expression of *c-myc* associated with Burkitt lymphoma translocations is specific to B cells and does not occur in other cell types (See Croce, supra, page

155, col. 2). In addition, the presence of truncated *TAN-1* RNA transcripts do not indicate whether the expression of encoded *TAN-1* protein or, in particular, molecules displaying Notch antigenicity (*e.g.*, fusion proteins or deletion mutants), is increased, decreased or remains the same, much less in a manner so as to provide diagnostic utility.

In fact, on page 658, col. 2 to page 659, col. 2, the authors of Ellisen speculate about the possible mechanisms by which the *TAN-1* translocation exerts an effect in lymphoblastic leukemia ("ALL"), mentioning the hypothetical possibilities that *TAN-1* acts as a tumor suppressor and one allele is lost while the other is inactivated, or that the translocation causes production of a *TAN-1* protein lacking the extracellular domain thereby inhibiting its cell adhesion function or uncoupling ligand-binding with growth-controlling signal transduction. It is clear that there is no teaching of a correlation between increased or decreased expression of a Notch protein, or molecule having Notch antigenicity, and the presence of a malignancy.

Moreover, Applicants emphasize that Ellisen also does not suggest a correlation between Notch and cervical, breast, lung, and colon cancers, melanomas and selanomas, and/or benign dysproliferative disorders. Ellisen discloses that: 1) *TAN-1* is predicted to encode *cdc10/SW16* repeats and that "the inference has been made that protein domains containing these repeats have some role in the control of cell growth and differentiation" (Ellisen, page 657, column 2), and 2) *TAN-1* RNA is detected in every normal human fetal and adult mouse tissue tested except the small intestine (Ellisen, Figure 5,

page 654). Applicants submit that this teaching and the disclosure that some T lymphoblastic leukemic cells have a translocation within *TAN-1* are insufficient to "suggest" that there is a correlation between aberrant Notch protein expression and cervical, breast, lung, and colon cancers, melanomas and selanomas, and/or benign dysproliferative disorders, and that such correlation can be used as the basis of a method of screening for such disorders.

Furthermore, Applicants submit that Ellisen does not suggest a correlation between Notch and diseases or disorders of the nervous system. Ellisen discloses that: 1) Drosophila Notch and other neurogenic genes of Drosophila are required for correct segregation of epidermal from neuronal cells during Drosophila embryogenesis (Ellisen, page 658, column 1), and 2) *TAN-1* RNA in detected in normal fetal brain tissue and normal adult mouse central nervous system tissue (Ellisen, page 653, column 2). Applicants submit that contrary to the Examiner's rejection, this disclosure and the disclosure that some T lymphoblastic leukemic cells have a translocation within *TAN-1* do not suggest that there is a correlation between aberrant Notch protein expression and disorders of the nervous system in humans.

Applicants further submit that the lack of guidance in Ellisen as to the function of *TAN-1* further evidences the lacking of teaching by this reference of any diagnostic screening methodology based on measuring levels of Notch protein or molecule having the antigenicity of a Notch protein. This lack of guidance is exemplified at page 658, of Ellisen wherein, in an attempt to explain the apparent

critical role of Notch in Drosophila embryogenesis and the effects of Notch mutants on larval and pupal stages, as well as the ubiquitous expression of *Notch* and *TAN-1* in fetal and adult tissues, the author opines "[a] reasonable explanation to reconcile these findings is that Notch, and possibly *TAN-1*, as well, act in diverse ways at different times during development and in different tissues."

Furthermore, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

A *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 26 U.S.P.Q.2d, 1529, 1531 (Fed. Cir. 1993). The art must suggest how to apply its teachings to the specifically claimed invention. Here, Applicants respectfully assert that the Ellisen reference does not suggest how to apply its teachings to achieve a method of screening for the presence of a malignancy, disease or disorder of the nervous system, or benign dysproliferative disorder, characterized by an increased or aberrant level of Notch protein or molecule having the antigenicity of a Notch protein in a patient.

Ellisen is not concerned with Applicants' problem. Ellisen teaches the characterization of the human *TAN-1* Notch homolog and the screening of cell lines known to be leukemic for the presence of a translocation break point in the *TAN-1* gene. Ellisen suggests, at best, that there may be a correlation between altered *TAN-1* RNA and a single type of lymphoblastic leukemia. Ellisen does not suggest doing what

Applicants have done. Ellisen cannot be properly extrapolated to or modified so as to provide for a method of screening for the presence of a malignancy, disease or disorder of the nervous system, or benign dysproliferative disorder, characterized by an increased or aberrant level of Notch protein or molecule having the antigenicity of a Notch protein in a patient.

The Examiner's attention is respectfully directed to *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (BPAI 1992). In Obukowicz, the Appellants' invention concerned a method of combatting plant insect pests using plant colonizing bacteria that had been genetically modified to produce the protein toxin of *B. thuringiensis*. The modified bacteria were applied to the plant and the expressed toxin was consumed by the plant pests.

In reversing the Examiner's rejection under 35 U.S.C. §103, the Board noted that:

> We are unable to find a suggestion [in the art] *to do* what appellants have done. *Id* at 1065.

In reviewing the art relied on by the Examiner, the Board dismissed one reference relied on by the Examiner stating that it was "replete with advice" but contained "little information regarding how to use the transformed bacteria and **clearly does not specifically suggest appellants' use.**" [Emphasis added.]

Applicants respectfully assert that the same could be said for the art cited in the instant application. As in Obukowicz, the cited art is not concerned with and does not suggest Applicants' method.

The Board continued:

> This specific statement regarding combatting mosquitos using genetically engineered "natural pond microflora" is relied on by the examiner for the "suggestion" required by the aforementioned case law. However, the specific statement by Dean is not a suggestion to insert the gene into the *chromosome* of bacteria *and* apply that bacteria to the plant environment in order to protect the plant. *Id* at 1965.

Applicants respectfully assert that in the instant case, as in Obukowicz, the cited art does not contain a specific suggestion as to the particular form of the claimed invention and how to achieve it. Furthermore, Applicants submit that Ellisen falls short of providing even general guidance for a diagnostic screen for the presence of a malignancy, disease or disorder of the nervous system, or benign dysproliferative disorder, characterized by an increased or aberrant level of Notch protein or molecule having antigenicity of a Notch protein in a patient. In Obukowicz, even such general guidance was found inadequate to render the invention obvious. *See also In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

As in Obukowicz, it is irrelevant that one can, in some embodiments, possibly theoretically explain the technological rationale for the claimed invention using selected teachings from the reference. The suggestion to do what Applicants have done comes only from the Examiner, after reading the blueprint provided by Applicants' specification. This approach has been repeatedly criticized as hindsight reconstruction. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir.

1991); *W.L. Gore & Assocs. Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 312-313 (Fed. Cir. 1983).

Therefore, the Ellisen reference not suggesting the particular form of the claimed invention and not specifically suggesting that the artisan do what Applicants have done, Applicants respectfully assert that *prima facie* obviousness is not established.

Applicants respectfully assert that they have obviated the rejection under 35 U.S.C. § 103 as a consequence of the arguments above. Accordingly, this rejection should be withdrawn. The same is believed proper, and is respectfully requested.

CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. In view of the above amendments and comments, it is believed that the Examiner's objections to the specification and rejections of the claims under 35 U.S.C. § 112, first and second paragraphs, and 35 U.S.C. § 103 have been overcome and that the present application is in condition for immediate allowance. Withdrawal of the Examiner's rejections and early notice to this effect is earnestly solicited. If any issues remain, the Examiner is respectfully

requested to telephone Adriane M. Antler to discuss the same.

Respectfully submitted,

Dated: 4-24-96

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